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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/958,570	10/28/97	GREGORY R	16930-000921

HM12/0124

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EXAMINER	
GUZO, D	
ART UNIT	**PAPER NUMBER**
1636	16

DATE MAILED: 01/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/958,570	GREGORY ET AL.	
	Examiner	Art Unit	
	Dave Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-24 26-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24 and 26-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 16-24 and 26-31, 33, 35, 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim methods of treating pathologies (i.e. cancers) via gene therapy protocols using claimed adenoviral vectors comprising a partial or total deletion of the protein IX gene and a gene encoding a functional anti-tumor gene (i.e. a tumor suppressor gene or suicide gene or suicide gene, such as HSV TK, and a thymidine kinase metabolite.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 Bd. App. & Inter. 1986 and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). These factors include the following;

1) Unpredictability of the art. The gene therapy art at the time the invention was made was extremely unpredictable. This unpredictability is manifested at the levels of vector design for *in*

vivo delivery of transgenes to target cells, the level of efficiently delivering the transgenes to target cells, the transient and unpredictable expression of transgenes in target cells, etc. (See Orkin et al., "Report to the NIH Panel", see whole document, particularly pp. 6-11; and Verma et al., Nature, Vol. 389, 9/18/97, pp. 239-242, see whole article, particularly pp. 239 and 241 for reviews). With regard to use of gene therapy protocols involving tumor suppressor genes and "pro-drug" based strategies for treatment of cancer, Ross et al. (Human Gene Therapy, Vol. 7, 1996, pp. 1781-1790, see whole article, particularly pp. 1783 and 1786) notes that these therapies are (years after applicants' invention) still totally experimental with little or no evidence of efficacy in patients. The reasons for failure of these therapies *in vivo* is not explained.

2) State of the art. The gene therapy art at the time of applicants' invention was poorly developed. As noted by Orkin et al. in 1995 and by Verma et al. in 1997, no gene therapy protocol had been unambiguously proven to be successful *in vivo*. With regard to use of adenoviral vectors for treatment of cancer, it is noted that Verma et al., as late as Sept. 1997, notes that use of adenoviral vectors to treat cancer is ***still only a "promising approach"*** which still apparently has not been reduced to practice in patients.

3) Number of working examples. Applicants present no working examples of the claimed invention.

4) Amount of guidance presented by applicants. Applicants present some *in vitro* data and *in vivo* data using nude mice bearing Hep3B tumors. However, it is unclear how these data relate to the treatment of cancers in patients and if this *in vitro* and mouse data is art recognized as being

reasonably predictive of results which would be expected in patients. Applicants' in the instant specification do not provide teachings whereby the skilled artisan would overcome the art recognized problems associated with successful practicing of gene therapy in patients and indeed, do not even address these critical issues.

5) Scope of the claims. The claims read broadly on treatment of any of thousands of different pathologies in animals or humans or potentially hundreds of different cancers in animals or humans. The scope of the claims must be considered to be extremely broad.

6) Nature of the invention. The invention involves one of the most complex, unpredictable areas of molecular biology and medicine, the use of gene therapy procedures to treat pathologies in humans or animals.

7) Level of skill in the art. The level of skill in the gene therapy art is very high; however, those of preeminent skill in the art were unable to reduce to practice successful gene therapy years after the priority date of applicants' invention.

The kit recited in claim 31 is included in this rejection because a kit for practicing a non-enabled invention is likewise not enabled.

Given the above analysis of the factors which the courts have indicated are critical in determining whether a given invention is enabled, it must be considered that the skilled artisan would have had to have practiced undue and excessive experimentation in order to practice the claimed invention.

3. Claims 32, 34, 36-37, 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for obtaining expression of a tumor suppressor gene or suicide protein in a cell *in vitro*, does not reasonably provide enablement for said method practiced *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rationale underlying the limitation of these claims to the *in vitro* environment is outlined in the above 35 USC 112, 1st paragraph rejection. The claims are not enabled for the *in vivo* embodiment for the reasons outlined in the above 35 USC 112, 1st paragraph rejection of claims 16-24, 26-31, 33, 35, 38 and 40.

No Claims are allowed.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard A. Schwartz, can be reached on (703) 308-1133. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams whose telephone number is (703) 305-3291.

David Guzo
January 22, 2001

DAVID GUZO
PRIMARY EXAMINER